REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the following remarks.

Rejection under 35 U.S.C. § 103

Claims 1-6, 10, 12 and 14-17 have been rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by Harigai et al. Pharmaceutical Research 18:1284-90, 2001 in view of Mayer et al., U.S. Patent No. 5,616,341. The rejection is traversed.

The Office has acknowledged the novelty of the claimed liposome preparation of the invention characterized by that pH of the interior aqueous phase wherein the drug is loaded is up to 5, and the membrane of the vesicle is modified with a hydrophilic macromolecule (PEG, for example) only on its exterior surface. The term "loading" is basically used to designate the state in which the drug is at least encapsulated in the closed space of the liposome. *See, e.g.*, DESCRIPTION [0048].

Harigai et al disclose a PEG-modified liposome, but never disclose a drug loaded therein. Rhodamine as being considered drug by the examiner is not a drug loaded in the closed space of the liposome. This may be seen from the descriptions of Harigai as being 'all components were dissolved, lyophilized, and then hydrated in physiologic saline' to prepare 'rhodamine-labeled' liposomes ("preparation of cationic liposomes", pp.1285).

Rhodamine used in Harigai etr al. is Lissamine rhodamine B 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (rhodamine DHPE) ("Material" pp.1285), that is a lipid derivative of rhodamine,

i.e. one of the components making up the membrane for fluorescence labeling.

More important is that the interior aqueous phase in Harigai et al is simply "physiologic saline" as above. The pH of the physiologic saline is not 'up to 5' and no other component for the interior aqueous phase is disclosed. Thus, Harigai et al not only fail to disclose an interior aqueous phase with pH 5 or less, but also fail to teach or suggest any reason to use an aqueous phase less that pH 5. The Office has acknowledged that Harigai et al. does not teach a pH of less than or loading a drug that is unstable at a pH greater than pH 5.

Indeed, stability of PEG- modified liposome preparations including a drug within an interior aqueous phase with pH 5 or less is never taught in Harigai et al. The investigation of Harigai et al is essentially relating to "binding ability between liposomes and cells" which is tested only in vitro, and has nothing to do with stability properties of liposomes, such as a retentivity in blood, membrane stability or a storage stability.

On the other hand, the liposome of Mayer et al is not modified with PEG. Mayer et al do not refer to modification of the membrane with PEG and certainly not on the outside surface only.

Mayer et al discuss the stability in blood (retentivity) of an unmodified liposome. The discussions, however, are entirely-focused on the release rate in the unmodified liposome, and make no reference to subjects such as stability when the membrane of liposome is modified. Thus, Mayer et al do not teach or suggest any reason to modify the membrane of a liposome as recited in the claims.

The disclosures of Harigai et al and Mayer et al are not combinable. Alone or

in combination, the documents could not lead one of ordinary skill in the art to an understanding of the relationship between the pH of the interior aqueous phase and membrane modification on the exterior with a hydrophilic macromolecule such as PEG. Without such an understanding, there could have been no rational basis for modifying the references to arrive at the claimed invention. There would be no reason to modify only the exterior surface of the liposome when it includes the interior aqueous phase at a pH of up to 5.

The rejection is based on a mere conclusory allegation of obviousness. However, as can be seen above, there is no apparent reason to have combined the Harigai and Mayer references. The Office has not addressed the factors required to support a finding of obviousness. The Office has not provided an explanation of how the teachings of the references are alleged to be interrelated; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all of which are required to determine whether there was an apparent reason to combine the known elements in the fashion claimed, which the Supreme Court has his said should be made explicit. *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) (*citing In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")).

Applicants maintain that for at least the reasons stated above, the prior art would not have provided a reason or suggestion to modify or combine the

references in the manner claimed. Thus, it would not have been obvious to have made the claimed invention.

Rejection under the Doctrine of Obviousness-Type Double Patenting

Claims 1-6, 10-12, and 14-17 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims of U.S. Patent No. 5,676,971. The rejection is traversed.

The Office has cited Harigai and Mayer, *supra*, as evidence of that it would have been obvious to have modified the patented invention to arrive at the presently claimed invention. However, as explained above, there is no teaching in Harigai or Mayer, separately, or combined that would provide a reason to make the presently claimed combination. For the same reasons, there would have been no reason to have modified the invention claimed in U.S. Patent No. 5,676,971 to have arrived at the invention now claimed but for the teaching of the present disclosure of, among other things, an understanding of the relationship between a modifying a liposome with PEG only on the outside surface, and the stability of loading a drug in an aqueous solution of pH5 or less on the interior of a liposome. Thus, the present invention is not obvious in view of the patented invention and is separately patentable.

CONCLUSION

Applicants invite the Examiner to contact Applicants' representative at the telephone number listed below if any issues remain in this matter, or if a discussion regarding any portion of the application is desired by the Examiner.

In the event that this paper is not timely filed within the currently set shortened statutory period, Applicants respectfully petition for an appropriate extension of time. The fees for such extension of time may be charged to our Deposit Account No. 02-4800. In the event that any additional fees are due with this paper, please charge our Deposit Account No. 02-4800.

Respectfully submitted,

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